

## REMARKS

Reconsideration and withdrawal of the rejections set forth in the Office action dated November 9, 2001 are respectfully requested. Applicants petition the Commissioner for a two-month extension of time in which to file this amendment. A separate petition is enclosed.

### I. Amendment

Claim 1 is amended to change the word 'compound' in the preamble to "agent" for consistency internally and with dependent claim 6.

Claim 9 is amended for internal consistency.

These minor amendments are made solely to place the claims in better form for appeal, and entry of the clarifications is respectfully requested.

### II. Rejections under 35 U.S.C. §102

Claims 1-2 were rejected under 35 U.S.C. §102(b) as allegedly anticipated by Mislick *et al.* (*Bioconjugate Chem.*, 6:512-515 (1995)).

Claims 1-2, 4-14, and 16-21 were rejected under 35 U.S.C. §102(b) as allegedly anticipated by Lee *et al.* (*Biochimica et Biophysica Acta*, 1233:134-144 (1995)).

Claims 1-2, 4-14, and 16-21 were rejected under 35 U.S.C. §102(b) as allegedly anticipated by Goren *et al.* (*Proceed. Intl. Symp. Control Rel. Bioact. Mater.*, 24:865-866 (1997)) or Horowitz *et al.* (Chemistry and Biology of Pteridines and Folates, Pfeleiderer and Rokos, eds., 11<sup>th</sup> Symposium, p. 353-356 Berlin, 1997).

Claims 1-3 and 13-15 were rejected under 35 U.S.C. §102(a) as allegedly anticipated by Brasier (U.S. Patent No. 5,804,445).

These rejections are respectfully traversed for the following reasons.

Summaries of Applicants' invention and of the cited documents are provided in the response submitted August 30, 2001.

## A. Analysis

### 1. Legal Standard for Novelty

To anticipate a claim, a prior art reference must disclose every limitation of the claimed invention, either expressly or inherently. M.P.E.P. § 2131.

### 2. Interpretation of the Present Claims

Only when a claim is properly understood can a determination be made whether the prior art anticipates and/or renders obvious the claimed invention. Claim 1 of the instant application reads:

1. A method of administering a therapeutic agent to a multi-drug resistant cell expressing P-glycoprotein, comprising
  - preparing a conjugate composed of (i) a carrier; (ii) a folate ligand attached to the carrier; and (iii) a therapeutic agent associated with the carrier; and
  - administering the conjugate to a subject;
  - whereby said administering is effective to achieve accumulation of said therapeutic agent in said cell.

The phrase "administering a therapeutic compound to a multi-drug resistant cell expressing P-glycoprotein" is technically part of the preamble, because it appears before the transitioning word "comprising." However, in this case, Applicants assert that the phrase is a claim limitation, since without treating the phrase as a claim limitation, the phrase "to achieve accumulation of said therapeutic agent in said cell" would not have proper antecedent basis.

Therefore, Applicants' invention relates to a method of administering a therapeutic compound to a multi-drug resistant cell to achieve accumulation of the agent in the multi-drug resistant cell.

Independent claim 9 in relevant part reads:

9. A method of administering to a multi-drug resistant cell a therapeutic compound which in free form does not accumulate in the cell, comprising, ...

....

....whereby accumulation of the compound in the cell is achieved in an amount sufficient for cytotoxicity of said cell.

Similar to claim 1, the phrase " administering to a multi-drug resistant cell a therapeutic compound" is part of the preamble, but must be taken to be a claim limitation to give meaning and antecedent basis to later recitation of "said cell." Thus, claim 9 relates to a method of administering a compound to a multi-drug resistant cell in such a way as to achieve accumulation of the compound in the cell in an amount sufficient for cytotoxicity.

### 3. Examiner's Position

In the Final Office action, the Examiner asserts that Applicant has incorrectly argued the Mislick *et al.* fails to teach a therapeutic agent. The Examiner has misread Applicants' argument. In the response submitted August 30, 2001 Applicant stated:

"Mislick *et al.* fail to teach or suggest element (3) of the method claim and element (4) of the composition claims." (Response submitted August 30, 2001, page 7, first full paragraph).

The three elements of the method claims are set forth in Applicants' response just prior to this sentence (Response submitted August 30, 2001, page 6) and are:

- (1) preparing a conjugate composed of (i) a carrier; (ii) a folate ligand attached to the carrier; and (iii) a therapeutic agent associated with the carrier; and
- (2) administering the conjugate to a subject;
- (3) whereby said administering is effective to achieve accumulation of the therapeutic agent in the cell (Response submitted August 30, 2001, page 6)

Element (3) of the method claim is not the therapeutic compound, but the limitation that "whereby said administering is effective to achieve accumulation of the therapeutic agent in the cell."

Due to the Examiner's misreading of Applicants' remarks, the Examiner has misunderstood Applicants' position with respect to all of the cited documents. Appropriate reconsideration is respectfully requested.

The Examiner also appears to misunderstand that the claimed subject matter relates to a method of overcoming multi-drug resistance in a cell. The Examiner is directed to the above discussion regarding claim interpretation.

#### 4. Summary of the Rejections based on the Cited Documents

Five documents are cited as anticipating references. Each of the documents relates in some way to the use of the folate-folate receptor system for targeting a therapeutic compound to a cell expressing the folate receptor. The majority of the documents relate to liposomal compositions having a folate targeting ligand (Lee *et al.*; Horowitz *et al.*; Goren *et al.*, Brazier *et al.*). One reference Mislick *et al.* relates to a folate-polylysine complex.

The Examiner, in making the rejections, does not elaborate on the basis of his position, and simply states what each document teaches (*e.g.*, "Mislick teaches the delivery of folate-polylysine-DNA complexes to carcinoma cell cultures."). However, the Examiner's remarks in the Final Office action suggest that no consideration has been given to the nature of the claimed subject matter, or if given, has not been communicated clearly to Applicants. That is, the Examiner does not appear to appreciate that a method of administering a compound to a multi-drug resistant cell is claimed, despite Applicants repeated remarks on this point in the August 30, 2001 response.

It is eminently clear from a reading of the five cited documents that none is concerned with a method of administering a compound to a multi-drug resistant cell. As discussed above, Applicants' claims expressly relate to a method of administering a compound to a multi-drug resistant cell and to achieving accumulation of the compound in such a cell. Since the cited art references do not expressly disclose these limitations of the claimed invention, the only remaining consideration is whether the cited art inherently discloses these limitations of the claimed invention.

#### 5. Relevant Case Law on Inherent Anticipation

A prior art reference may inherently anticipate a claimed invention, even if the reference does not expressly disclose the claimed invention. The Court of Appeals for the Federal Circuit (CAFC) announced in *Continental Can Co. v. Monsanto Co.* (948 F.2d 1264; 20 USPQ2d 1746 (Fed. Cir. 1991)) a two prong test to find inherent anticipation. In the first prong, inherent anticipation requires that the undisclosed element of the prior art had to be a necessary technological

fact of the prior art. The second prong requires that persons of ordinary skill in the art recognize the undisclosed element as a natural consequence of the prior art.

This issue of inherent anticipation was again recently addressed by the CAFC in *Rapoport v. Dement* (254 F.3d 1053; 59 USPQ2d 1215 (Fed. Cir. 2001)), where Appellant Rapoport argued the Board of Patent Appeals and Interference erred in not finding the claims to the opposing party, Dement, inherently anticipated by a prior art publication. Both Rapoport and Dement had pending applications with claims to a "method for treatment of sleep apnea" by administration of certain azapirone compounds, such as buspirone, to a patient in need of such treatment. After declaration of an interference, Rapoport alleged the subject matter of the count was not patentable to Dement, the senior party, on the grounds it was anticipated and/or rendered obvious by a prior publication authored by Rapoport.

Rapoport's prior publication disclosed treatment of anxiety by administration of buspirone, and suggested that treatment with buspirone had potential as a primary treatment for dyspnea, or difficulty in breathing in general. Since anxiety is a known secondary symptom of sleep apnea, Rapoport asserted that while the publication did not disclose administering buspirone with the intent of treating sleep apnea per se, such an explicit intent is not necessary in order to anticipate the claim of Dement corresponding to the count. Rapoport argued that as long buspirone was administered to a patient for treatment of anxiety, and that patient had sleep apnea, the reference was anticipatory to a claim to a method of treating sleep apnea.

The Court disagreed, finding there was no disclosure in Rapoport's publication of administration of buspirone to patients suffering from sleep apnea with the intent to cure the underlying condition. The data in Rapoport's prior publication was limited to treatment with buspirone to patients suffering from anxiety, not from sleep apnea. Thus, the court affirmed the Board's conclusion that the Rapoport publication (i) did not disclose administration of buspirone to patients suffering from sleep apnea to treat sleep apnea and, therefore (ii) did not inherently anticipate a claim to a method of treating sleep apnea by administration of buspirone.

#### 6. Application of Case Law to Instant Claims

The instant claims relate to a method of administering an agent to a multi-drug resistant cell by delivering the agent in the form of a conjugate comprised of the agent and a folate-targeted carrier. Cited against the claims are prior art documents disclosing an agent associated with a

folate-polymer or entrapped in a folate-targeted liposome. Like *Rapoport*, the compound is disclosed in the prior art (*i.e.*, buspirone in *Rapoport*; an agent associated with a folate-targeted carrier here). However, also like the facts in *Rapoport*, the cited prior art fails to show or suggest the claimed method of treatment. That is, there is no disclosure in any of the cited documents of administering an agent in the form of a folate-targeted carrier to a multi-drug resistant cell with the intent to overcome the multi-drug resistance and to achieve accumulation of the agent in the cell.

The teaching in the cited Mislick *et al.* reference is limited to a method of intracellular delivery of DNA by complexing the DNA with a folate-polylysine carrier. There is no disclosure relating to a method of administering a compound to a multi-drug resistant cell.

Lee *et al.* disclose folate-targeted liposomes for delivery of doxorubicin to epithelial tumor cells. There is no teaching or suggestion in Lee *et al.* of administration of a folate-targeted drug conjugate to a multi-drug resistant cell.

Goren *et al.* pertain to folate-targeted liposomes for the delivery of doxorubicin to tumor cells. There is no teaching or suggestion in Goren *et al.* of a method of administering an agent to a multi-drug resistant cell.

Horowitz *et al.* relate to folate-targeted liposomes for delivery to tumors. Horowitz *et al.* fail to teach or suggest a method of administering an agent to a multi-drug resistant cell.

Brasier relates to the administration of a polypeptide, and in one embodiment, in combination with a folate-conjugated liposome. Brasier nowhere shows or suggests a method of administering an agent to a multi-drug resistant cell.

Accordingly, Applicants submit that the present claims are not anticipated by the cited documents, and respectfully request withdrawal of the rejections under 35 U.S.C. §102.

### III. Rejections under 35 U.S.C. §103

Claims 1-2, 4-14, and 16-21 were rejected under 35 U.S.C. §103 as allegedly obvious over Lee *et al.* or Goren *et al.* or Horowitz *et al.*

Claims 1-3, and 13-16 were rejected under 35 U.S.C. §103 as allegedly obvious over Mislick *et al.* or Brasier in view of Lee *et al.* or Goren *et al.* or Horowitz *et al.* individually or in combination.

These rejections are respectfully traversed.

A. Analysis

To establish a prima facie case of obviousness, the prior art references (or references when combined) must teach or suggest all the claim limitations. M.P.E.P. § 2143.

As discussed above, Applicants' claims relate to a method of administering an agent to a multi-drug resistant cell. The cited documents fail to show or suggest a method of administering an agent to a multi-drug resistant cell by administering a folate-targeted drug conjugate, or that such a method would be effective to achieve accumulation of the agent in a multi-drug resistant cell.

With respect to the rejection over Lee *et al.* or Goren *et al.* or Horowitz *et al.*, these references are silent on the problem of multi-drug resistance, and nowhere suggest a method for administering an agent to a multi-drug resistant cell or a means to accumulate an agent in such a cell.

The same arguments apply to the rejection over Mislick *et al.* or Brasier, in view of Lee *et al.* or Goren *et al.* or Horowitz *et al.* Namely, none of the references either alone or in combination show or suggest a method for administering an agent to a multi-drug resistant cell or for achieving accumulation of an agent in such a cell.

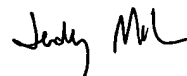
Accordingly, Applicants respectfully request withdrawal of the rejections under 35 U.S.C. §103.

IV. CONCLUSION

In view of the above remarks, Applicants submit that the claims now pending are in condition for allowance. A Notice of Allowance is, therefore, respectfully requested.

The Examiner is invited to contact Applicants' representative at 650-838-4402 if it is believed that prosecution of this application may be assisted thereby.

Respectfully submitted,



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Date: April 8, 2002

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**VERSION WITH MARKINGS TO SHOW CHANGES MADE**

1. (Twice Amended) A method of administering a therapeutic [compound] agent to a multi-drug resistant cell expressing P-glycoprotein, comprising  
 preparing a conjugate composed of (i) a carrier; (ii) a folate ligand attached to the carrier; and (iii) a therapeutic agent associated with the carrier; and  
 administering the conjugate to a subject;  
 whereby said administering is effective to achieve accumulation of said therapeutic agent in said cell.

9. (Amended) A method of administering to a multi-drug resistant cell a therapeutic compound which in free form does not accumulate in the cell, comprising,  
 preparing liposomes composed of (i) vesicle-forming lipids and including a vesicle forming lipid derivatized with a hydrophilic polymer chain having a free distal end, (ii) a folate ligand attached to the free distal end of at least a portion of the hydrophilic polymer chains, and (iii) a therapeutic agent entrapped in the liposomes; and  
 administering the liposomes to a subject;  
 whereby accumulation of the compound in the cell is achieved in an amount sufficient for [cell] cytotoxicity of said cell.